



<PRORULE>

<PREAMB>

4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 866

[Docket No. FDA-2012-N-0159]

Microbiology Devices; Reclassification of Nucleic Acid-Based Systems for Mycobacterium tuberculosis Complex

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify nucleic acid-based in vitro diagnostic devices for the detection of Mycobacterium tuberculosis complex in respiratory specimens from class III (premarket approval) into class II (special controls). These devices are intended to be used as an aid in the diagnosis of pulmonary tuberculosis.

DATES: Submit either electronic or written comments by [INSERT DATE 90 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER]. See section IX of this document for the proposed effective date of any final rule that may publish based on this proposal.

ADDRESSES: You may submit comments, identified by Docket No. FDA-2012-N-0159, by any of the following methods:

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: <http://www.regulations.gov>. Follow the instructions for submitting comments.

### Written Submissions

Submit written submissions in the following ways:

- FAX: 301-827-6870.
- Mail/Hand delivery/Courier (for paper or CD-ROM submissions): Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

Instructions: All submissions received must include the Agency name and Docket No. FDA-2012-N-0159 for this rulemaking. All comments received may be posted without change to <http://www.regulations.gov>, including any personal information provided. For additional information on submitting comments, see the "Comments" heading of the SUPPLEMENTARY INFORMATION section of this document.

Docket: For access to the docket to read background documents or comments received, go to <http://www.regulations.gov> and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Division of Dockets Management, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

Janice A. Washington,  
Center for Devices and Radiological Health,  
Food and Drug Administration,  
10903 New Hampshire Ave.,  
Bldg. 66, rm. 5554,

Silver Spring, MD 20993-0002,  
301-796-6207.

#### SUPPLEMENTARY INFORMATION:

##### I. Regulatory Authorities

The Federal Food, Drug, and Cosmetic Act (the FD&C Act), as amended by the Medical Device Amendments of 1976 (the 1976 amendments) (Public Law 94-295), the Safe Medical Devices Act of 1990 (Public Law 101-629), and the Food and Drug Administration Modernization Act of 1997 (FDAMA) (Public Law 105-115), the Medical Device User Fee and Modernization Act of 2002 (Public Law 107-250), the Medical Devices Technical Corrections Act (Public Law 108-214), and the Food and Drug Administration Amendments Act of 2007 (Public Law 110-85), establish a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the FD&C Act (21 U.S.C. 360c) established three categories (classes) of devices, reflecting the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under the FD&C Act, FDA clears or approves the three classes of medical devices for commercial distribution in the United States through three regulatory processes: Premarket approval (PMA), product development protocol, and premarket notification (a premarket notification is generally referred to as a "510(k)" after the section of the FD&C Act where the requirement is found). The purpose of a premarket notification is to demonstrate that the new device is substantially equivalent to a legally-marketed predicate device. Under section 513(i) of the FD&C Act, a device is substantially equivalent if it has the same intended use and technological characteristics as a predicate device, or has different technological characteristics

but data demonstrate that the new device is as safe and effective as the predicate device and does not raise different issues of safety or effectiveness.

FDA determines whether new devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the FD&C Act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807) of the regulations. Section 510(k) of the FD&C Act and the implementing regulation part 807, subpart E, require a person who intends to market a medical device to submit a premarket notification submission to FDA before proposing to begin the introduction, or delivery for introduction into interstate commerce, for commercial distribution of a device intended for human use.

In accordance with section 513(f)(1) of the FD&C Act, devices that were not in commercial distribution before May 28, 1976, the date of enactment of the 1976 amendments, generally referred to as postamendment devices, are classified automatically by statute into class III without any FDA rulemaking process. These devices remain in class III and require premarket approval, unless the device is classified or reclassified into class I or class II, or FDA issues an order finding the device to be substantially equivalent, in accordance with section 513(i) of the FD&C Act, to a predicate device that does not require premarket approval. The Agency determines whether new devices are substantially equivalent to predicate devices by means of premarket notification procedures in section 510(k) of the FD&C Act and part 807 of FDA's regulations.

Devices of a new type that FDA has not previously classified based on risk are "automatically" or "statutorily" classified into class III by operation of section 513(f)(1) of the FD&C Act, regardless of the level of risk they pose. This is because, by definition, a new type of device would not be within a type that was on the market before the 1976 Medical Device

Amendments or that has since been classified into class I or class II. Congress enacted section 513(f)(2) of the FD&C Act as part of FDAMA. The process created by this provision, which is referred to in FDAMA as the Evaluation of Automatic Class III Designation, will be referred to as the "de novo process". Congress included this section to limit unnecessary expenditure of FDA and industry resources that could occur if lower risk devices were subject to premarket approval under section 515 of the FD&C Act (21 U.S.C. 360e).

Reclassification of classified postamendment devices is governed by section 513(f)(3) of the FD&C Act. This section provides that FDA may initiate the reclassification of a device classified into class III based under section 513(e) of the FD&C Act. FDA's regulations in § 860.130 (21 CFR 860.130) set forth the procedures for the filing and review of a petition for reclassification of such class III devices. In order to change the classification of the device, it is necessary that the proposed new class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

## II. Regulatory Background of the Device

Nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens is a postamendment device classified into class III under section 513(f)(1) of the FD&C Act in 1995. Consistent with the FD&C Act and FDA's regulations in § 860.130(a), FDA believes that these devices should be reclassified from class III into class II because there is sufficient information from FDA's accumulated experience with these devices to establish special controls that can provide reasonable assurance of the device's safety and effectiveness.

## III. Identification

Nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens are qualitative nucleic acid-based in vitro diagnostic devices intended to detect M. tuberculosis complex nucleic acids extracted from human respiratory specimens. These devices are non-multiplexed and intended to be used as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings. These devices do not include devices intended to detect the presence of organism mutations associated with drug resistance. Respiratory specimens may include sputum (induced or expectorated), bronchial specimens (e.g., bronchoalveolar lavage or bronchial aspirate), or tracheal aspirates.

#### IV. Background for Reclassification Decision

At an FDA/Centers for Disease Control (CDC)/National Institute of Allergy and Infectious Diseases (NIAID) public workshop entitled "Advancing the Development of Diagnostic Tests and Biomarkers for Tuberculosis," held in Silver Spring, MD, on June 7 and 8, 2010 (Ref. 1), the class III designation for nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens was raised as a barrier to advancing M. tuberculosis diagnostics. Based on discussion at the public workshop, FDA agreed to consider this issue further and subsequently convened a meeting of the Microbiology Devices Panel of the Medical Devices Advisory Committee (Microbiology Devices Panel) on June 29, 2011 (Ref. 2). Although not a formal reclassification meeting, panel members were asked to discuss if sufficient risk mitigation was possible for FDA to initiate the reclassification process from class III to class II devices for this intended use through the drafting of a special controls guidance. The panel was not asked to vote on whether actual reclassification should occur or to

assess whether any previously approved device or specific device currently under development warranted reclassification.

All panel members expressed the opinion that sufficient data and information exists such that the risks of false positive and false negative results can be mitigated to allow a special controls guidance to be created that would support reclassification from class III to class II for nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens. All outside speakers at the open public hearing session during the meeting also spoke in favor of reclassification.

#### V. Classification Recommendation

FDA is proposing that nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens be reclassified from class III to class II. FDA believes that class II with special controls (guidance document and limitations on the distribution) would provide reasonable assurance of the safety and effectiveness of the device. Section 510(m) of the FD&C Act provides that a class II device may be exempt from the premarket notification requirements under section 510(k), if the Agency determines that premarket notification is not necessary to provide reasonable assurance of the safety and effectiveness of the device. For this device, FDA believes that premarket notification is necessary to provide reasonable assurance of safety and effectiveness and, therefore, does not intend to exempt the device from the premarket notification requirements.

#### VI. Risks to Health

After considering the information discussed by the Microbiology Devices Panel during the June 29, 2011, meeting, the published literature, and the Medical Device Reporting system reports, FDA believes the following risks are associated with nucleic acid-based in vitro

diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens: (1) False positive test results may lead to incorrect treatment of the individual with possible adverse effects. The patient may be subjected to unnecessary isolation and/or other human contact limitations. Unnecessary contact investigations may also occur; (2) False negative test results could result in disease progression, and the risk of transmitting disease to others.; and (3) Biosafety risks to healthcare workers handling specimens and control materials with the possibility of transmission of tuberculosis infection to healthcare workers.

## VII. Summary of the Reasons for Reclassification

FDA, consistent with the opinions expressed by the Microbiology Devices Panel of the Medical Devices Advisory Committee, believes that the establishment of special controls, in addition to general controls, provides reasonable assurance of the safety and effectiveness of nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens.

1. The safety and effectiveness of nucleic acid-based systems for M. tuberculosis complex have become well-established since approval of the first device for this use in 1995.

2. The risk of false positive test results can be mitigated by specifying minimum performance standards in the special controls guidance and including information regarding patient populations appropriate for testing in the device labeling. Additional risk mitigation strategies include the indication for use that the device be used as an aid to the diagnosis of pulmonary tuberculosis in conjunction with other clinical and laboratory findings. The device also should be accurately described and have labeling that addresses issues specific to these types of devices.



3. The risk of false negative test results can be mitigated by specifying minimum performance standards for test sensitivity in the special controls guidance and ensuring that different patient populations are included in clinical trials. Additional risk mitigation strategies include the indication for use that the device be used as an aid to the diagnosis of pulmonary tuberculosis in conjunction with other clinical and laboratory findings. The device also should be accurately described and have appropriate labeling that addresses issues specific to these types of devices.

4. Biosafety risks to healthcare workers handling specimens and control materials with the possibility of transmission of tuberculosis infection to healthcare workers could be addressed similarly to existing devices of this type that we have already approved. It is believed there are no additional biosafety risks introduced by reclassification from class III to class II. The need for appropriate biosafety measures can be addressed in labeling recommendations that are included in the special controls guidance and by adherence to recognized laboratory biosafety procedures.

Based on FDA's review of published literature, the information presented by outside speakers invited to the Microbiology Devices Panel meeting, and the opinions of panel members expressed at that meeting, FDA believes that there is a reasonable basis to determine that nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens can provide the significant benefit of rapid detection of infection in patients with suspected tuberculosis as compared to traditional means of diagnosis. For patients with acid-fast smear negative tuberculosis, nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens are currently the only laboratory tests available for rapid detection of active pulmonary tuberculosis. Rapid identification of patients

with active tuberculosis may have significant benefits to the infected patient by earlier diagnosis and management as well as potentially significant effects on the public health by limiting disease spread.

Nucleic acid-based in vitro diagnostic devices for the detection of M. tuberculosis complex in respiratory specimens have been approved for marketing by FDA for over 15 years. There is substantial scientific and medical information available regarding the nature, complexity, and problems associated with these devices. Revised public health recommendations for use, published by CDC on January 16, 2009, recommended the use of nucleic acid amplification testing in conjunction with acid-fast microscopy and culture and specifically states that "Nucleic acid amplification testing should be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary [tuberculosis] for whom a diagnosis of [tuberculosis] is being considered but has not yet been established, and for whom the test result would alter case management or [tuberculosis] control activities" (Ref. 3).

#### VIII. Special Controls

FDA believes that, in addition to general controls, the proposed special controls discussed in this document are adequate to address the risks to health.

FDA believes that the draft guidance document entitled "Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of Mycobacterium tuberculosis Complex in Respiratory Specimens," will address the risks previously identified in this document and provide a reasonable assurance of safety and effectiveness of the device. The class II special controls guidance document provides information on how to meet premarket (510(k)) submission requirements for the device in sections that discuss analytical performance studies, performance studies using clinical specimens, and labeling. FDA believes that the class II special controls

guidance document, which incorporates analytical studies, performance standards, and labeling statements and recommendations, minimizes risks to health and provides reasonable assurance of device safety and effectiveness.

Elsewhere in this issue of the Federal Register, FDA is publishing a notice of availability of this class II special controls guidance document that the Agency intends to use for this device.

Table 1.--Risks to Health and Mitigation Measures

Identified Risks	Recommended Mitigation Measures
False positive test results may lead to incorrect treatment of the individual with possible adverse effects. The patient may be subjected to unnecessary isolation and/or other human contact limitations. Unnecessary contact investigations may also occur.	Device Description Performance Studies Labeling
False negative test results could result in disease progression and the risk of transmitting disease to others.	Device Description Performance Studies Labeling
Biosafety risks to healthcare workers handling specimens and control materials with the possibility of transmission of tuberculosis infection to healthcare workers.	Labeling

#### IX. Proposed Effective Date

FDA proposes that any final rule based on this proposal become effective 30 days after its date of publication in the Federal Register.

#### X. Environmental Impact

The Agency has determined under 21 CFR 25.34(b) that this proposed reclassification action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

#### XI. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct Agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Agency believes that this proposed rule is not a significant regulatory action as defined by the Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the proposed rule would create no new burdens, the Agency proposes to certify that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is \$136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this proposed rule to result in any 1-year expenditure that would meet or exceed this amount.

Our estimate of benefits annualized over 20 years is \$9.4 million at a 3-percent discount rate and \$7.4 million at a 7-percent discount rate. The change in pre and postmarketing requirements between a 510(k) and a PMA lead to benefits in the form of reduced submission

costs, review-related activities, and inspections. Another unquantifiable benefit from the rule is that a decrease in entry could lead to further product innovation. FDA is unable to quantify the costs that could arise if there is a change in risk which could lead to adverse events, recalls, warning letters, or unlisted letters.

The full discussion of economic impacts (Ref. 4) is available in docket FDA-2012-N-0159 and at <http://www.regulations.gov>.

## XII. Federalism

FDA has analyzed this proposed rule in accordance with the principles set forth in Executive Order 13132. Section 4(a) of the Executive order requires Agencies to "construe \*\*\* a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority under the Federal statute." Federal law includes an express preemption provision that preempts certain state requirements "different from or in addition to" certain Federal requirements applicable to devices. (See section 521 of the FD&C Act (21 U.S.C. 360k); Medtronic, Inc. v. Lohr, 518 U.S. 470 (1996); and Riegel v. Medtronic, Inc. 128 S. Ct. 999 (2008)). If this proposed rule is made final, the special controls established by the final rule would create "requirements" for specific medical devices under 21 U.S.C. 360(k), even though product sponsors have some flexibility in how they meet those requirements (Cf. Papike v. Tambrands, Inc., 107 F.3d 737, 740-742 (9th Cir. 1997)).

### XIII. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no new collections of information. Therefore, clearance by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) is not required.

This proposed rule designates a draft guidance document as a special control. FDA also tentatively concludes that the draft special control guidance document does not contain new information collection provisions that are subject to review and clearance by OMB under the PRA. Elsewhere in this issue of the Federal Register, FDA is publishing a notice announcing the availability of that draft guidance document entitled "Class II Special Controls Guidance Document: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of Mycobacterium tuberculosis Complex in Respiratory Specimens," which contains an analysis of the paperwork burden for the draft guidance.

### XIV. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

### XV. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not

responsible for any subsequent changes to the Web sites after this document publishes in the Federal Register.)

1. Transcript of the Tuberculosis Public Workshop, June 7, 2010, (Available at <http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/CriticalPathInitiative/UpcomingEventsonCPI/UCM289182.doc>, accessed on January 25, 2012).

2. Transcript of FDA's Microbiology Devices Panel Meeting, June 29, 2011, (Available at <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/MicrobiologyDevicesPanel/UCM269469.pdf>.)

3. "Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis," Morbidity and Mortality Weekly Report (MMWR), vol. 58(1), pp. 7-10, January 16, 2009, (Available at <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm>, accessed on July 26, 2011).

4. Full Disclosure Preliminary Regulatory Impact Analysis Initial Regulatory Flexibility Analysis Unfunded Mandates Reform Act Analysis.

#### List of Subjects in 21 CFR Part 866

Biologics, Laboratories, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 866 be amended as follows:

#### PART 866--IMMUNOLOGY AND MICROBIOLOGY DEVICES

1. The authority citation for part 866 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Add § 866.3372 to subpart D to read as follows:

§ 866.3372 Nucleic acid-based in vitro diagnostic devices for the detection of *Mycobacterium tuberculosis* complex in respiratory specimens.

(a) Identification. Nucleic acid-based in vitro diagnostic devices for the detection of *Mycobacterium tuberculosis* complex in respiratory specimens are qualitative nucleic acid-based in vitro diagnostic devices intended to detect *M. tuberculosis* complex nucleic acids extracted from human respiratory specimens. These devices are non-multiplexed and intended to be used as an aid in the diagnosis of pulmonary tuberculosis when used in conjunction with clinical and other laboratory findings. These devices do not include devices intended to detect the presence of organism mutations associated with drug resistance. Respiratory specimens may include sputum (induced or expectorated), bronchial specimens (e.g., bronchoalveolar lavage or bronchial aspirate), or tracheal aspirates.

(b) Classification. Class II (special controls). The special control for this device is the FDA document entitled "Class II Special Controls Guidance Document: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens." For availability of the guidance document, see § 866.1(e).

Dated: March 13, 2012.

Leslie Kux,

Acting Assistant Commissioner for Policy.



<BILCOD>BILLING CODE 4164&ndash;01&ndash;P

[FR Doc. 2012-6518 Filed 03/16/2012 at 8:45 am; Publication Date: 03/19/2012]